

Serum neurofilament light in atrial fibrillation: clinical, neuroimaging and cognitive correlates

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Running Title: Neurofilament light in atrial fibrillation

Characters in Title: 97

Characters in Running Title: 38

Word Count Abstract: 374

Word Count Manuscript (excluding references): 5,427

References: 50

Figures: 5, Tables: 3

Supplementary Material: Figures: 1, Tables: 4

Abstract

Emerging evidence suggests that atrial fibrillation is associated with cognitive dysfunction independently of stroke, but the underlying mechanisms remain unclear. In this cross-sectional analysis from the Swiss-AF Study (NCT02105844), we investigated the association of serum neurofilament light protein, a neuronal injury biomarker, with (i) the CHA₂DS₂-VASc score (congestive heart failure, hypertension, age 65-74 or ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, sex), clinical and neuroimaging parameters and (ii) cognitive measures in atrial fibrillation patients.

We measured neurofilament light in serum using an ultrasensitive single-molecule array assay in a sample of 1,379 atrial fibrillation patients (mean age 72 years, 27% female). Ischemic infarcts, small vessel disease markers and normalized brain volume were assessed on brain MRI. Cognitive testing included the Montreal Cognitive Assessment, Trail Making Test, Semantic Verbal Fluency and Digit Symbol Substitution Test, which were summarized using principal component analysis. Results were analyzed using univariable and multivariable linear regression.

Neurofilament light was associated with the CHA₂DS₂-VASc score, with an average 19.2% (95% confidence interval [17.2%, 21.3%]) higher neurofilament per unit CHA₂DS₂-VASc increase. This association persisted after adjustment for age and MRI characteristics. In multivariable analyses, clinical parameters associated with neurofilament light were higher age (32.5% [27.2%, 38%] neurofilament increase per 10 years), diabetes mellitus, heart failure and peripheral artery disease (26.8% [16.8%, 37.6%], 15.7% [8.1%, 23.9%] and 19.5% [6.8%, 33.7%] higher neurofilament, respectively). Mean arterial pressure showed a curvilinear association with neurofilament, with evidence for both an inverse linear and a U-shaped association. MRI characteristics associated with neurofilament were white matter lesion volume and volume of large non-cortical or cortical infarcts (4.3% [1.8%, 6.8%] and 5.5% [2.5%, 8.7%] neurofilament increase per unit increase in log-volume of the respective lesion), as well as normalized brain volume (4.9% [1.7%, 8.1%] higher neurofilament per 100 cm³ smaller brain volume). Neurofilament light was inversely associated with all cognitive measures in univariable analyses. The effect sizes diminished after adjusting for clinical and MRI variables, but the association with the first principal component was still evident.

Our results suggest that in atrial fibrillation patients, neuronal loss measured by serum neurofilament light is associated with age, diabetes mellitus, heart failure, blood pressure and vascular brain lesions, and inversely correlates with normalized brain volume and cognitive function.

Keywords: neurofilament light, atrial fibrillation, vascular brain lesions, cognition

Abbreviations: AF, atrial fibrillation; AIC, Akaike's information criterion; BMI, body mass index; CI, confidence interval; DSST, Digit Symbol Substitution Test; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; LNCCIs, large non-cortical or cortical infarcts; MAP, mean arterial pressure; MBs, microbleeds; MoCA, Montreal Cognitive Assessment; MPRAGE, magnetization-prepared rapid gradient echo; nBV, normalized brain volume; PC1, first principal component; PAD, peripheral artery disease; SD, standard deviation; SNCIs, small non-cortical infarcts; sNfL, serum neurofilament light; SVF, Semantic Verbal Fluency; SWI, susceptibility-weighted imaging; TIA, transient ischemic attack; TMT, Trail Making Test

Introduction

Atrial fibrillation (AF) and dementia are highly prevalent in the elderly. AF is linked to dementia through ischemic stroke, but evidence has emerged that even in the absence of clinically manifest stroke, the risk of cognitive impairment and dementia is increased in patients with AF (Chen *et al.*, 2018; Madhavan *et al.*, 2018; Kim *et al.*, 2019). Several potential mechanisms have been postulated to explain this association, including silent cerebral infarcts, cerebral small vessel disease (through shared risk factors such as diabetes and hypertension) and cerebral hypoperfusion (Madhavan *et al.*, 2018; Diener *et al.*, 2019), but tangible evidence is lacking. With the progressive ageing of the population, AF and dementia are a continuously growing public health concern, and a deeper understanding of the pathophysiological pathways underlying their association will be crucial in developing strategies to preserve cognitive function in the elderly (Kuhne *et al.*, 2019).

In a cross-sectional analysis from the Swiss Atrial Fibrillation (Swiss-AF) cohort study, we previously showed that cortical and large non-cortical infarcts were common in AF patients and were independently associated with a lower score on the Montreal Cognitive Assessment (MoCA), lending support to the hypothesis that cognitive dysfunction in AF might – at least in part – be mediated through covert cerebral embolic infarcts (Conen *et al.*, 2019).

Here, we used serum neurofilament light protein (sNfL) to further explore the mechanisms that underly neuronal damage and cognitive dysfunction in AF. Neurofilaments are neuron-exclusive cytoskeletal proteins that are released in the extracellular space, cerebrospinal fluid and eventually peripheral blood following neuroaxonal damage. sNfL has emerged as a biomarker for neuronal injury in inflammatory, degenerative, traumatic and vascular neurological disorders (Khalil *et al.*, 2018), but has not yet been investigated as a marker of neurological disease in AF. In this analysis from the Swiss-AF cohort study we investigated the association of sNfL with (i) clinical parameters and neuroimaging characteristics and (ii) measures of cognitive function.

Materials and methods

Study design, patient population and data collection

This was a cross-sectional analysis using baseline data from the ongoing prospective observational Swiss-AF cohort study (NCT02105844), that enrolled 2,415 AF patients between 2014 and 2017 across 14 centers in Switzerland. The detailed methodology of Swiss-AF has been described previously (Conen *et al.*, 2017; Conen *et al.*, 2019). In short, Swiss-AF included patients with documented AF aged 65 years or older, with an additional 15% of patients aged between 45 and 65 years. Patients with secondary forms of AF, those with a recent ischemic stroke, transient ischemic attack (TIA) or other acute illness (< 4 weeks) and those unable to provide informed consent (e.g., patients with dementia, psychosis or delirium) were excluded. Baseline information on sociodemographic parameters and comorbidities was collected based on patients' history and/or medical chart review as applicable, using standardized case report forms. Upon inclusion, weight, height and the mean of 3 consecutive blood pressure measurements were obtained, and patients underwent blood sampling, brain MRI and cognitive testing.

Baseline blood samples were collected following standard operating procedures (Conen *et al.*, 2017). After centrifugation, serum samples were aliquoted into cryotubes and stored at -80°C in a centralized biobank. sNfL concentrations were measured in duplicate using a previously described ultrasensitive single-molecule array assay (Disanto *et al.*, 2017). Inter-assay coefficients of variation were 10% for low (mean, 6.9 pg/mL), 12% for medium (mean, 19.6 pg/mL) and 5% for high (mean, 84.5 pg/mL) concentration quality control serum samples measured in duplicate in every run. The mean intra-assay coefficient of variation of duplicate determinations for concentration was 5%. Individuals performing sNfL measurements were blinded to clinical, MRI and cognitive patient data.

Baseline brain MRI was acquired on a 1.5 or 3.0 Tesla scanner using a standardized protocol including a 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE), a 2D axial fluid-attenuated inversion recovery (FLAIR), a 2D axial diffusion-weighted imaging (DWI) and a 2D axial susceptibility-weighted imaging (SWI) or T2*-weighted sequence (Conen *et al.*, 2017; Conen *et al.*, 2019). All scans were analyzed centrally in a core lab (Medical Image Analysis Center AG, Basel, Switzerland) by expert raters blinded to clinical and cognitive patient data and sNfL measurements. We evaluated the following vascular brain lesions, which we defined adapting the STRIVE classification of small vessel disease (Wardlaw *et al.*, 2013), as in previous

research (Conen *et al.*, 2019): (i) Small non-cortical infarcts (SNCIs), defined as hyperintense lesions on FLAIR, ≤ 20 mm in diameter on axial sections and not involving the cortex, consistent with ischemic infarction in the territory of a perforating arteriole and located in the white matter, internal or external capsule, deep brain nuclei, thalamus or brainstem. (ii) Large non-cortical infarcts were non-cortical infarcts with a diameter > 20 mm. Cortical infarcts were defined as FLAIR hyperintense lesions involving the cortex irrespective of their size and whether they also involved subcortical areas. Large non-cortical and cortical infarcts (LNCCIs) were grouped together in the analyses. All infarcts were characterized as recent (hyperintense) or chronic according to their appearance on DWI. (iii) FLAIR hyperintensities not meeting the aforementioned criteria for infarcts were identified as white matter lesions (WMLs). (iv) Microbleeds (MBs) were identified and counted as nodular, strongly hypointense lesions on either SWI or T2*-weighted sequences. T2-weighted volumes of SNCIs, LNCCIs and WMLs were segmented and quantified semi-automatically in mm³ using Amira (Mercury Computer Systems Inc., Chelmsford, Massachusetts). Lesions with a central FLAIR hypointense core were segmented in total without differentiating between hyperintense and hypointense lesion areas. The normalized brain volume (nBV) was estimated in cm³ on MPRAGE using SIENAX (Smith *et al.*, 2002).

Cognitive testing was performed by trained study personnel in a standardized manner and included:

- (i) the MoCA, which assesses visuospatial and executive functions, confrontation naming, memory, attention, language and abstraction. Subjects could obtain a maximum of 30 points, with higher scores indicating better cognitive function. One point was added to the test score if the patient had ≤ 12 years of formal education (Nasreddine *et al.*, 2005).
- (ii) the Trail Making Test (TMT), which assesses visual attention, processing speed and executive functioning. It consists of two parts (A and B), in which the subject was instructed to connect a set of 25 points, either circled numbers in ascending order (TMT-A) or circled numbers and letters in alternating numeric and alphabetic ascending order (TMT-B), as quickly as possible while maintaining accuracy. The number of correct connections and the time to test completion in seconds were measured, with a maximum allowed time of 180 and 300 seconds for TMT-A and TMT-B, respectively. The test metric was the number of correct answers per second, with higher scores indicating better cognitive function (Tombaugh, 2004).
- (iii) semantic verbal fluency (SVF), which assesses semantic memory and language production. Subjects were asked to name as many words as possible from the semantic category “animals”

within 60 seconds. The test metric was the number of correct responses, with higher scores indicating better cognitive function (Morris *et al.*, 1989).

- (iv) the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale, which assesses processing speed, visuomotor coordination and attention. The subject received a key grid of numbers and matching symbols and a test section with numbers and empty boxes. The test consisted of filling as many empty boxes as possible with the matching symbol from the key grid. The score was the number of correct number-symbol matches achieved within 120 seconds, with higher scores indicating better cognitive function (Petermann, 2011).

The detailed patient flowchart for the analyses of this study is given in Supplementary Figure 1. We included all Swiss-AF patients with quantifiable sNfL measurement and complete MRI data and excluded those with recent subclinical ischemic infarcts on DWI (which would expectedly raise sNfL concentrations disproportionately (Gattringer *et al.*, 2017; De Marchis *et al.*, 2018; Tiedt *et al.*, 2018)). The Ethics Committee of Northwest and Central Switzerland approved Swiss-AF including the present study (PB_2016-00793). Written informed consent was obtained from all study participants according to the Declaration of Helsinki. This study was conducted in accordance with the STROBE Statement for cross-sectional studies (von Elm *et al.*, 2007).

Statistical analyses

Analysis A: Association of the CHA₂DS₂-VASc score, clinical and MRI characteristics with sNfL

To investigate the association of patients' characteristics with sNfL, we fitted uni- and multivariable linear regression models with various sets of clinical and MRI variables as independent variables and the log-transformed sNfL concentration as dependent variable. Continuous independent variables were centered on their mean (or, in case of skewed data, median) values. We report the back-transformed model-based estimates, which represent multiplicative effects on the geometric mean of sNfL and are denoted by β_{mult} (so that a one-unit increase in the independent variable is associated with an average β_{mult} -fold change in sNfL), along with 95% confidence intervals (CI) and two-sided p-values. We interpret p-values as a continuous measure, with smaller values indicating stronger evidence for an association, but without specifying a threshold value. To compare between models, we used the Akaike's information criterion (AIC), which estimates the relative quality of different models fitted to a given dataset, while penalizing models for larger number of independent variables. Lower AIC values indicate a better fit. Additionally, we provide the coefficient of determination (R^2) of each model as a measure of the

proportion of the observed sNfL variance explained by the model. Since R^2 tends to increase with the number of independent variables, we also provide the adjusted R^2 (R^2_{adj}), which penalizes R^2 for larger numbers of variables. We fitted the following predefined models with log-sNfL as the dependent variable:

- (i) the CHA₂DS₂-VASc score (congestive heart failure, hypertension, age 65-74 or ≥ 75 years, diabetes mellitus, stroke or TIA, vascular disease, sex) models: CHA₂DS₂-VASc is a validated clinical score predicting stroke risk in AF patients (Lip *et al.*, 2010; Friberg *et al.*, 2012). We opted to first investigate the association of sNfL with this risk score as a whole, independent of its individual components. Given the known association of sNfL with age (Khalil *et al.*, 2018), we fitted univariable models for the association of sNfL with age, with the CHA₂DS₂-VASc score and with the CHA₂DS₂-VASc score after exclusion of its age component. Additionally, we fitted bivariable models for the age-adjusted association of sNfL with the CHA₂DS₂-VASc score and with the CHA₂DS₂-VASc score after exclusion of its age component. We selected the best fitting CHA₂DS₂-VASc score model based on AIC values, and proceeded to further adjust it for MRI markers of small vessel disease (SNCIs, MBs and WMLs) (Wardlaw *et al.*, 2013) as well as for all MRI variables, as detailed below, in two additional multivariable models.
- (ii) the clinical model: We fitted a multivariable model for the association of sNfL with the following predefined clinical variables: age, sex, history of hypertension, diabetes mellitus, stroke or TIA, coronary heart disease, peripheral artery disease (PAD), heart failure, obstructive sleep apnea, AF type (paroxysmal, persistent, permanent), body mass index (BMI, calculated as weight in kg / height in m²), smoking status (active, past, non-smoker), alcohol consumption (number of standard drinks daily) and mean arterial pressure (MAP, calculated as $1/3 * \text{systolic blood pressure} + 2/3 * \text{diastolic blood pressure}$ (DeMers and Wachs, 2019)). We opted to use the MAP instead of including both systolic and diastolic blood pressure in the models due to collinearity between those variables. There was no evidence of collinearity upon visual inspection of scatter plots for any of the other continuous clinical variables, but there was evidence for a curvilinear association between sNfL and MAP, which we modelled by introducing an additional quadratic term (MAP²). We reduced the clinical model to a smaller set of variables via stepwise backward elimination based on AIC values. We imputed the few missing values in the clinical variables with simple single imputation, using the mode (i.e., the most common category) for categorical variables and the mean (or, in case of skewed data, the median) for continuous variables (Table 1; one missing value in smoking status and

alcohol consumption, imputed with “past” and 0.6 standard drinks daily, respectively; six missing values in systolic and diastolic blood pressure, imputed with 134.7mmHg and 78.4mmHg, respectively).

- (iii) the MRI model: We fitted a multivariable model for the age-adjusted association of sNfL with the following predefined MRI variables: nBV, SNCIs’ presence and log-transformed volume, LNCCIs’ presence and log-volume, MBs’ presence and count (truncated at 20 to reduce the influence of outliers) and WMLs’ log-volume.
- (iv) the combined clinical and MRI model: We fitted a final combined model for the association of sNfL with the chosen clinical and all MRI variables from the models (ii) and (iii).

Analysis B: Association of sNfL with measures of cognitive function

To investigate the association of sNfL with cognitive function we fitted linear regression models with the score of each of the cognitive tests (MoCA, TMT-A, TMT-B, SVF, DSST) as the dependent variable and the log-transformed sNfL concentration as independent variable. We report the model-based estimates, which represent additive effects on the mean of the test score and are denoted by β , along with the 95%CI and two-sided p-values. A one-unit increase in log-sNfL is associated with an average change in the test score of β units (or a 10% increase in sNfL is associated with a change of $0.095 * \beta$ units in the test score). For each cognitive test we fitted the following predefined models with test score as the dependent variable:

- (i) univariable model (including only log-sNfL as independent variable)
- (ii) age-adjusted model (including log-sNfL and age as independent variables)
- (iii) clinical multivariable model, including log-sNfL, age, sex, education level (basic, middle, advanced), history of hypertension, diabetes mellitus, stroke or TIA, coronary heart disease, PAD, heart failure, obstructive sleep apnea, BMI, smoking status (active, past, non-smoker) and alcohol consumption (number of standard drinks daily) as independent variables. We imputed the few missing values in the clinical variables with simple single imputation, as described above.
- (iv) MRI multivariable model, including log-sNfL, age, nBV, SNCIs’ presence and log-volume, LNCCIs’ presence and log-volume, burden of MBs (categorized as 0, 1, 2 and ≥ 3) and WMLs’ log-volume as independent variables
- (v) combined clinical and MRI multivariable model, including all aforementioned variables

To summarize performance over all cognitive tests we used principal component analysis. The first principal component (PC1) explained 61.3% of the observed variance and the loading of each test on PC1 (representing the covariance between each test and PC1) was positive (MoCA: +0.40, TMT-A: +0.45, TMT-B: +0.50, SVF: +0.39, DSST: +0.49), thereby allowing for the use of PC1 as a single, summary measure of cognitive function, with higher values indicating better cognitive performance. We additionally fitted all models (i) – (v) described above with PC1 as the dependent variable.

As a sensitivity analysis, we repeated all models described under analyses A and B in the subset of patients without history of stroke or TIA.

All analyses were performed with R version 3.5.2 (2018-12-20) (R Core Team, 2019).

Data availability

The Swiss-AF consent forms, as approved by the ethics committee, do not allow for the data to be made publicly available. Researchers may contact the authors for the potential submission of research proposals for future analyses or independent verification of our results.

Results

A total of 1,379 patients (mean [SD] age 72.3 [8.6] years, 27.1% female) with quantifiable sNfL measurement and complete MRI data were available for analysis A (Supplementary Figure 1). The median (IQR) sNfL concentration was 38.2 (26.6 – 56.4) pg/ml. The detailed demographic, clinical and MRI characteristics of all patients are presented in Table 1.

Association of the CHA₂DS₂-VASc score with sNfL

The CHA₂DS₂-VASc score was associated with sNfL in univariable analysis, with an average 19.2% increase in sNfL concentration per point increase in the CHA₂DS₂-VASc score ($\beta_{\text{mult}} = 1.192$, 95%CI [1.172, 1.213], $p < 0.001$; Figure 1). Age was also strongly associated with sNfL in univariable analysis ($\beta_{\text{mult}} = 1.489$ per 10 years, 95%CI [1.440, 1.539], $p < 0.001$). The association between the CHA₂DS₂-VASc score and sNfL persisted after excluding the age component of the score, after adjusting for age and after both excluding the age component and adjusting for age. The model with the best fit was the one including the unmodified CHA₂DS₂-VASc score and adjusting for age, which was used in the rest of the analyses. The CHA₂DS₂-VASc score remained associated with sNfL after adjusting for MRI markers of small vessel disease and for all MRI variables combined (Supplementary Table 1).

Association of clinical and MRI characteristics with sNfL

The detailed results of the clinical, MRI and combined models are given in Table 2. The clinical model fitted the data better and explained a larger proportion of the observed sNfL variance compared to the MRI model. The combined clinical and MRI model fitted the data best. Figure 2 shows the effect size estimates for the association of all clinical and MRI variables with sNfL from the combined model: Parameters positively associated with sNfL were age (on average 32.5% higher sNfL per 10 years), history of diabetes mellitus (26.8% higher sNfL), PAD (19.5% higher sNfL) and heart failure (15.7% higher sNfL), as well as volume of LNCCIs and WMLs (5.5% and 4.3% higher sNfL per unit increase in log-volume of the respective lesion). MAP showed a curvilinear association with sNfL, with an inverse linear and U-shaped component (Figure 3A). Parameters inversely associated with sNfL were BMI (7.3% lower sNfL per 5kg/m² higher BMI), past smoker status (7% lower sNfL compared to non-smoker), alcohol consumption (1.9% lower sNfL per 1 standard drink daily) and nBV (4.9% lower sNfL per 100 cm³ larger nBV; Figure 3B).

Association of the sNfL with measures of cognitive function

Of the 1,379 patients with sNfL and MRI data, cognitive testing was incomplete in 16, leaving 1,363 patients available for analysis B. The median (IQR) MoCA score was 26 (24 – 28) points, TMT-A and TMT-B scores were 0.53 (0.39 – 0.68) and 0.21 (0.14 – 0.28) correct connections per second, respectively, SVF score was 19 (15 – 23) correct responses and DSST score was 45 (36 – 54) correct matches. The detailed results of all models for the association of sNfL with all cognitive measures are presented in Table 3. In univariable analyses, log-sNfL was strongly associated with all cognitive tests and the PC1, with higher sNfL concentrations indicating worse cognitive performance. The effect sizes generally diminished for all cognitive measures after adjusting for age, clinical variables and MRI characteristics. In the combined models adjusting for all aforementioned parameters, the association of log-sNfL with TMT-A, TMT-B and PC1 persisted. Figure 4 shows the model-based estimates for the association of sNfL with PC1. The scatter plot of the association of sNfL with PC1 is presented in Figure 5.

Sensitivity analyses in patients without history of stroke or transient ischemic attack

After excluding those with history of stroke or TIA, 1,125 patients were available for sensitivity analysis A. Their median (IQR) sNfL concentration was 36.7 (25.5 – 53.2) pg/ml and their detailed demographic, clinical and MRI characteristics are presented in Table 1. Of those, 12 patients had incomplete cognitive testing, leaving 1,113 patients available for the sensitivity analysis B. Both sensitivity analyses in patients without history of stroke or TIA yielded consistent results with the main analysis (Supplementary Tables 2, 3 and 4).

Discussion

This cross-sectional study on the clinical, neuroimaging and cognitive correlates of sNfL in a large sample of AF patients showed the following key findings: (i) Higher CHA₂DS₂-VASc scores indicated increasing neuronal injury, independent of age and vascular brain lesions visible on MRI. (ii) Besides age, clinical factors associated with increased neuronal loss were diabetes mellitus, PAD, heart failure and lower MAP. (iii) MRI characteristics associated with higher sNfL were higher volume of WMLs and LNCCIs, as well as lower nBV. (iv) sNfL was associated with worse cognitive performance, an association which was largely but not exclusively explained by age, comorbidities and vascular brain lesions.

The CHA₂DS₂-VASc score, a validated clinical score predicting ischemic stroke risk in AF patients (Lip *et al.*, 2010; Friberg *et al.*, 2012), was associated with sNfL. This was independent of age, history of stroke and ischemic infarcts visible on MRI, as well as MRI markers of small vessel disease, and might therefore reflect ongoing ischemic brain injury in AF that evades detection on conventional MRI (Brundel *et al.*, 2012). Higher CHA₂DS₂-VASc scores have previously also been associated with an increasing risk for dementia in stroke-free AF patients (Kim *et al.*, 2019).

Our study in AF patients confirms the strong independent association of sNfL with age, which has been demonstrated across a wide variety of patient populations and healthy controls, probably reflecting neurodegenerative processes associated with normal ageing (Khalil *et al.*, 2018; Khalil *et al.*, 2020). Furthermore, we found that diabetes mellitus was associated with a sNfL increase by a similar magnitude as 10 years of age. In line with this, poor glycemic control was independently associated with sNfL in a previous study on sNfL among diabetics (Korley *et al.*, 2019). The association of diabetes mellitus with sNfL was independent of small vessel disease markers and potentially embolic infarcts on MRI. It remains therefore unknown whether this association reflects increasing ischemic neuronal injury in the presence of diabetes mellitus due to microinfarcts that go undetected on conventional MRI (Brundel *et al.*, 2012), some other non-ischemic, diabetes-induced mechanism of neuronal damage in the central nervous system (Malone, 2016) or the potential contribution of diabetic neuropathy in the peripheral nervous system (Mariatto *et al.*, 2018). Peripheral artery disease was another independent determinant of sNfL, even after adjustment for vascular MRI brain lesions, which might again reflect increasing

ischemic brain injury that evades detection on conventional MRI (Brundel *et al.*, 2012) in the presence of manifest atherosclerotic disease and is in line with cumulating evidence for the association of PAD with cognitive dysfunction independently of manifest cerebrovascular disease (Rafnsson *et al.*, 2009).

Interestingly, we found a curvilinear association of MAP with sNfL, with evidence for both an inverse linear and a U-shaped relationship, indicating increasing neuronal loss with lower MAP. This novel finding is in contrast to a previous smaller study in diabetics, which found a positive linear association of systolic blood pressure and no association of diastolic blood pressure with sNfL (Korley *et al.*, 2019). Since MAP is a measure of the organ perfusion pressure (DeMers and Wachs, 2019), our finding suggests that neuronal damage in AF may be partly attributable to cerebral hypoperfusion. This was independent of history of heart failure, which was another independent determinant of sNfL, suggesting that hemodynamic changes in AF might adversely affect brain health above and beyond clinically manifest heart failure. Taken together, these findings refine and further support the hypoperfusion hypothesis for the association of AF with cognitive dysfunction (Madhavan *et al.*, 2018; Diener *et al.*, 2019), which has been proposed based on the known associations of cerebral hypoperfusion with dementia (Austin *et al.*, 2011; Wolters *et al.*, 2017; Iadecola *et al.*, 2019), AF with cerebral hypoperfusion (Lavy *et al.*, 1980; Gardarsdottir *et al.*, 2017), and heart failure with cerebral hypoperfusion (Roy *et al.*, 2017) and cognitive dysfunction (Vogels *et al.*, 2007). Of note, recent studies in healthy individuals provide evidence for a U-shaped association of blood pressure with cognitive dysfunction (Lv *et al.*, 2017) and for an inverse association of diastolic blood pressure with white matter disease (Fuhrmann *et al.*, 2019) and cognitive decline (Levine *et al.*, 2019). Putting our findings in this context, the curvilinear association of MAP with sNfL that we observed might not be specific to AF, but rather reflect a universal effect of blood pressure on brain health.

Of all vascular MRI brain lesions, the volume of WMLs and chronic LNCCIs were the strongest independent determinants of sNfL, also after excluding patients with stroke history. This indicates that both small vessel disease and infarcts of potentially embolic origin, even clinically silent ones, contribute to neuronal injury in AF. Our finding is in line with previous research on the association of sNfL with the burden of small vessel disease (Gattringer *et al.*, 2017; Duering *et al.*, 2018; Uphaus *et al.*, 2019) and the size of acute ischemic infarcts (Gattringer *et al.*, 2017; Tiedt *et al.*,

2018), and might suggest a greater severity of ongoing neurodegenerative processes secondary to ischemia (Tiedt *et al.*, 2018) or persistent, active microischemic phenomena in the brain of AF patients with a higher burden of established, embolic or microangiopathic, ischemic MRI lesions. These findings demonstrate the potential of sNfL as a blood biomarker to select AF patients that would benefit from further MRI investigations to uncover potential subclinical vascular brain disease, considering that mass screening with MRI is not feasible and that sNfL in our cohort appeared to be sensitive to potential mechanisms of brain injury independent of structural changes visualized on MRI. Of note, the presence of MBs was only marginally associated with sNfL after adjustment for other brain lesions, an association that was further weakened in the combined model. Thus, MBs might represent a proxy marker of vascular brain disease and contribute little if any to neuronal injury *per se*, in line with previous observations (Akoudad *et al.*, 2016; Conen *et al.*, 2019).

Another major finding was the inverse association of normalized brain volume with sNfL, which was independent of age, history of stroke and vascular MRI brain lesions. This association, which has been described in neurological diseases including multiple sclerosis and dementias (Khalil *et al.*, 2018), might reflect an underlying ongoing neurodegenerative process in AF. Indeed, AF has been previously associated with reduced brain volume independent of ischemic infarcts, with putative explanations being cerebral microinfarcts or hypoperfusion leading to brain atrophy (Stefansdottir *et al.*, 2013; Piers *et al.*, 2016).

Despite the in-depth neuroimaging patient characterization, the clinical model still explained a larger proportion of the sNfL variance than the MRI model. We can only speculate on the reasons for this: It is possible that microischemic, hemodynamic, degenerative or other, yet unknown processes lead to neuronal damage in AF while remaining undetected on conventional MRI.

Finally, sNfL was inversely associated with cognitive performance in AF patients. This is in line with previous research on the association of sNfL with cognitive measures in patients with small vessel (Duering *et al.*, 2018) and neurodegenerative diseases (Byrne *et al.*, 2017; Mattsson *et al.*, 2017; Lin *et al.*, 2018; van der Ende *et al.*, 2019), and suggests that sNfL is a nondisease-specific marker of neuronal damage resulting in cognitive dysfunction. The association of sNfL with cognitive measures grew markedly weaker after adjusting for age and was further attenuated in the multivariable clinical and MRI models, indicating that a multitude of factors including ageing,

comorbidities and vascular brain lesions contribute to or mediate the association of neuronal damage with cognitive dysfunction in AF. Importantly, the association of sNfL with PC1, the summary cognitive measure, persisted after adjustment for all clinical and neuroimaging parameters, suggesting that additional unknown factors might contribute to this association. Among the separate cognitive measures, the strongest associations of sNfL were with TMT-A, TMT-B and – to a lesser extent – DSST, all measures of executive function, processing speed and attention. Preferential changes in these cognitive domains are known to reflect a vascular profile of cognitive dysfunction (O'Brien *et al.*, 2003) and have been previously associated with AF (Nishtala *et al.*, 2018).

The strengths of our study include (i) its large sample size of AF patients with detailed clinical, neuroimaging and cognitive characterization, allowing for adjustment for several confounding factors and thus reducing the risk of spurious findings, (ii) the standardized manner of data acquisition, high rate of data completeness and blinded MRI assessment and sNfL measurement, reducing the risk of bias and (iii) its multicenter design, indicating a certain generalizability of our results, at least within the Caucasian population of central Europe. However, the following limitations must be acknowledged: (i) The study's cross-sectional design, which allows only for assessment of association but not causality thereof. (ii) As Swiss-AF included exclusively AF patients, we did not have a comparison group of patients with other heart diseases or healthy controls. It is therefore unknown whether our results are specific to AF. (iii) A large number of Swiss-AF patients did not undergo brain MRI due to contraindications or claustrophobia and were thus ineligible for this study. It is therefore unknown whether our results are generalizable to AF patients unsuited for brain MRI. (iv) We were not able to adjust our analyses for diseases of the peripheral nervous system, which were not systematically collected in Swiss-AF but might contribute to sNfL (Khalil *et al.*, 2018). (v) Neuroimaging was performed on 1.5 or 3.0 Tesla scanners, which might miss a relevant proportion of microinfarcts compared to higher resolution MRI (van Veluw *et al.*, 2013).

In conclusion, our study demonstrates the potential of sNfL as a tool to explore the mechanisms that underly cognitive dysfunction in AF. It seems likely that neuronal damage in AF results from a complex interplay between subclinical brain ischemia, altered hemodynamics and neurodegeneration. sNfL holds promise not only as an instrument to investigate the intricate

mechanisms underlying the heart-brain interactions, but also as a surrogate outcome parameter for brain health and cognitive function in cardiovascular research. In future Swiss-AF analyses we plan to investigate the prognostic significance of sNfL and other blood-based biomarkers of cardiovascular disease longitudinally with regards to the development of vascular brain lesions, brain atrophy and cognitive dysfunction over time.

Acknowledgments

We would like to thank all Swiss-AF investigators, listed in the Appendix, for their contributions in data collection.

Funding

Swiss-AF was supported by grants from the Swiss National Science Foundation (33CS30_148474, 33CS30_177520), the Foundation for Cardiovascular Research Basel and the University of Basel. This study was supported by the Science Funds (Wissenschaftspool), Medical Division of the University Hospital Basel, Switzerland. David Conen holds a McMaster University Department of Medicine Mid-Career Research Award. His work is supported by the Hamilton Health Sciences RFA Strategic Initiative Program.

Competing interests

UF: Research grants for the Swiss National Science Foundation, Swiss Heart Foundation, Medtronic; Consultant for Stryker, Medtronic and CSL Behring; GMDM: support from the Swiss National Science Foundation; Spezialprogramm Nachwuchsförderung Klinische Forschung, University of Basel; Science Funds (Wissenschaftspool) of the University Hospital Basel; Swiss Heart Foundation; Bangerter-Rhyner-Stiftung; Swisslife Jubiläumsstiftung for Medical Research; Swiss Neurological Society; consulting honoraria by Bayer and BMS/Pfizer; speaker honoraria by Bayer and Medtronic; LHB: grants from the Swiss National Science Foundation, University of Basel, Swiss Heart Foundation, Stroke Association, AstraZeneca; consulting and advisory board fees from Amgen, Bayer, Bristol-Myers Squibb, Claret Medical; The other authors have no competing interests to declare.

Supplementary material

Supplementary material is available at Brain Communications online.

Appendix

List of all Swiss-AF investigators according to participating center:

University Hospital Basel and University of Basel: Stefan Osswald, Michael Kühne, Stefanie Aeschbacher, Chloe Auberson, Steffen Blum, Leo Bonati, Selinda Ceylan, David Conen, Simone Doerpfeld, Ceylan Eken, Marc Girod, Peter Hämmerle, Philipp Krisai, Michael Kühne, Christine Meyer-Zürn, Pascal Meyre, Andreas U. Monsch, Christian Müller, Stefan Osswald, Philipp

Reddiess, Anne Springer, Fabienne Steiner, Christian Sticherling, Thomas Szucs, Gian Voellmin, Leon Zwimpfer; **University Hospital Bern:** Nicolas Rodondi, Drahomir Aujesky, Urs Fischer, Juerg Fuhrer, Laurent Roten, Simon Jung, Heinrich Mattle; Luise Adam, Carole Elodie Aubert, Martin Feller, Claudio Schneider, Axel Loewe, Elisavet Moutzouri, Tanja Flückiger, Cindy Groen, Damiana Rakovic, Rylana Wenger, Lukas Ehram, Alexandra Nuoffer, Nathalie Schwab. **Triemli Hospital Zurich:** Andreas Müller, Christopher Beynon, Roger Dillier, Michèle Deubelbeiss, Franz Eberli, Christine Franzini, Isabel Juchli, Claudia Liedtke, Jacqueline Nadler, Thayze Obst, Noreen Tynan, Xiaoye Schneider, Katrin Studerus, Dominik Weishaupt; **Cantonal Hospital Baden:** Jürg-Hans Beer, Simone Fontana, Silke Kuest, Karin Scheuch, Denise Hischier, Nicole Bonetti, Alexandra Grau, Jonas Villinger, Eva Laube, Philipp Baumgartner, Mark Filipovic, Marcel Frick, Giulia Montrasio, Stefanie Leuenberger, Franziska Rutz; **Cardiocentro Lugano:** Tiziano Moccetti, Angelo Auricchio, Adriana Anesini, Cristina Camporini, Giulio Conte, Maria Luce Caputo, Francois Regoli; **Cantonal Hospital St.Gallen:** Peter Ammann, Roman Brenner, David Altmann, Michaela Gemperle; **Cantonal Hospital Fribourg:** Daniel Hayoz, Mathieu Firmann, Sandrine Foucras; **Cantonal Hospital Lucerne:** Richard Kobza, Benjamin Berte, Virginia Justi, Frauke Kellner-Weldon, Brigitta Mehmman, Myriam Roth, Andrea Ruckli-Kaeppli, Ian Russi, Kai Schmidt, Mabelle Young, Melanie Zbinden; **EOC Ospedale Regionale di Lugano:** Giorgio Moschovitis, Jane Frangi-Kultalahti, Anica Pin, Luisa Vicari; **University Hospital Geneva:** Dipen Shah, Georg Ehret, Hervé Gallet, Elise Guillermet, Francois Lazeyras, Karl-Olof Lovblad, Patrick Perret, Philippe Tavel, Cheryl Teres; **University Hospital Lausanne:** Jürg Schläpfer, Nathalie Lauriers, Marie Méan, Sandrine Salzmann; **Public Hospital Solothurn:** Frank-Peter Stephan, Andrea Grêt, Jan Novak, Sandra Vitelli; **EOC Ospedale San Giovanni di Bellinzona:** Marcello Di Valentino, Jane Frangi-Kultalahti, Augusto Gallino; **University Hospital Zurich and University of Zurich:** Fabienne Witassek, Matthias Schwenkglens; **Medical Image Analysis Center AG:** Jens Würfel, Anna Altermatt, Michael Amann, Petra Huber, Esther Ruberte, Tim Sinnecker, Vanessa Zuber; **Clinical Trial Unit Basel:** Michael Coslovsky, Pascal Benkert, Gilles Dutilh, Milica Markovic, Patrick Simon; **Schiller AG:** Ramun Schmid

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Table 1 Patient demographic, clinical and MRI characteristics

| | All patients (N = 1,379) | | Patients without stroke/TIA (N = 1,125) |
|--|-----------------------------|------------------------|--|
| demographic and clinical data | | missing values rate | |
| age, years, mean (SD) | 72.3 (8.6) | 0 % | 71.7 (8.8) |
| sex, female, N (%) | 374 (27.1) | 0 % | 297 (26.4) |
| AF-type, N (%) | | 0 % | |
| paroxysmal | 636 (46.1) | | 510 (45.3) |
| persistent | 408 (29.6) | | 349 (31.0) |
| permanent | 335 (24.3) | | 266 (23.6) |
| history of | | | |
| hypertension, N (%) | 930 (67.4) | 0 % | 741 (65.9) |
| diabetes mellitus, N (%) | 190 (13.8) | 0 % | 146 (13.0) |
| stroke or transient ischemic attack, N (%) | 254 (18.4) | 0 % | 0 (0) |
| coronary heart disease, N (%) | 364 (26.4) | 0 % | 292 (26.0) |
| peripheral artery disease, N (%) | 87 (6.3) | 0 % | 64 (5.7) |
| heart failure, N (%) | 297 (21.5) | 0 % | 238 (21.2) |
| obstructive sleep apnea, N (%) | 171 (12.4) | 0 % | 128 (11.4) |
| CHA ₂ DS ₂ -VASc score, median (IQR) | 3 (2 – 4) | 0 % | 3 (2 – 4) |
| smoking status, N (%) | | 0.1 % | |
| non-smoker | 603 (43.8) | | 488 (43.4) |
| past smoker | 671 (48.7) | | 553 (49.2) |
| active smoker | 104 (7.5) | | 84 (7.5) |
| alcohol consumption, standard drinks / day, median (IQR) | 0.6 (0.1 – 1.3) | 0.1 % | 0.6 (0.1 – 1.3) |
| education level, N (%) | | 0.1 % | |
| basic | 157 (11.4) | | 128 (11.4) |
| middle | 679 (49.3) | | 555 (49.3) |
| advanced | 541 (39.3) | | 442 (39.3) |
| body mass index, kg/m ² , mean (SD) | 27.5 (4.6) | 0 % | 27.6 (4.7) |
| systolic blood pressure, mmHg, mean (SD) | 134.7 (18.7) | 0.4 % | 134.7 (18.6) |
| diastolic blood pressure, mmHg, mean (SD) | 78.4 (11.9) | 0.4 % | 78.7 (11.9) |
| mean arterial pressure, mmHg, mean (SD) | 97.2 (12.6) | 0.4 % | 97.3 (12.7) |
| oral anticoagulation, N (%) | 1,240 (89.9) | 0 % | 1,004 (89.2) |
| MRI data | | | |
| small non-cortical infarcts, N (%) | 293 (21.2) | 0 % | 200 (17.8) |
| volume (if present), mm ³ , median (IQR) | 60 (30 – 150) | | 56 (30 – 123) |
| large non-cortical and cortical infarcts, N (%) | 288 (20.9) | 0 % | 153 (13.6) |
| volume (if present), mm ³ , median (IQR) | 1,374 (252 – 7,454) | | 585 (162 – 4,002) |
| white matter lesions, N (%) | 1,368 (99.2) | 0 % | 1,116 (99.2) |
| volume (if present), mm ³ , median (IQR) | 3,662 (1,350 – 9,197) | | 3,335 (1,224 – 8,252) |
| microbleeds, N (%) | 291 (21.1) | 0 % | 220 (19.6) |
| count (if present), median (IQR) | 1 (1 – 2) | | 1 (1 – 2) |
| normalized brain volume, cm ³ , median (IQR) | 1,411 (1,354 – 1,478) | 0 % | 1,417 (1,358 – 1,487) |

SD, standard deviation; IQR, interquartile range

Table 2: Association of patients' clinical and MRI characteristics with sNfL

| Variables (N = 1,379) | Clinical model* | | MRI model | | Combined model | |
|--|--|---------|--|---------|--|---------|
| | AIC = 2079.05 R ² = 0.36, R ² _{adj} = 0.36 | | AIC = 2148.29 R ² = 0.33, R ² _{adj} = 0.32 | | AIC = 2040.56 R ² = 0.39, R ² _{adj} = 0.38 | |
| | $\beta_{\text{mult}}^{\dagger}$ [95% CI] | p-value | $\beta_{\text{mult}}^{\dagger}$ [95% CI] | p-value | $\beta_{\text{mult}}^{\dagger}$ [95% CI] | p-value |
| age (per 10 years) | 1.411 [1.365, 1.460] | < 0.001 | 1.367 [1.312, 1.424] | < 0.001 | 1.325 [1.272, 1.380] | < 0.001 |
| BMI (per 5 kg/m ²) | 0.925 [0.897, 0.955] | < 0.001 | | | 0.927 [0.899, 0.957] | < 0.001 |
| MAP (per 10 mmHg) | 0.961 [0.939, 0.983] | < 0.001 | | | 0.958 [0.937, 0.980] | < 0.001 |
| MAP ² (per 10 mmHg) | 1.019 [1.008, 1.031] | 0.001 | | | 1.019 [1.007, 1.030] | 0.002 |
| history of hypertension | 1.068 [1.003, 1.138] | 0.042 | | | 1.030 [0.967, 1.098] | 0.351 |
| history of diabetes mellitus | 1.283 [1.181, 1.394] | < 0.001 | | | 1.268 [1.168, 1.376] | < 0.001 |
| history of stroke or TIA | 1.137 [1.059, 1.220] | < 0.001 | | | 1.056 [0.978, 1.141] | 0.166 |
| history of peripheral artery disease | 1.231 [1.098, 1.380] | < 0.001 | | | 1.195 [1.068, 1.337] | 0.002 |
| history of heart failure | 1.181 [1.102, 1.266] | < 0.001 | | | 1.157 [1.081, 1.239] | < 0.001 |
| past smoker (ref: non-smoker) | 0.925 [0.873, 0.980] | 0.008 | | | 0.930 [0.878, 0.984] | 0.012 |
| active smoker (ref: non-smoker) | 0.950 [0.850, 1.060] | 0.358 | | | 0.944 [0.847, 1.053] | 0.301 |
| alcohol consumption (per 1 standard drink daily) | 0.984 [0.965, 1.002] | 0.086 | | | 0.981 [0.963, 1.000] | 0.045 |
| presence of LNCCIs | | | 1.100 [1.025, 1.180] | 0.008 | 1.049 [0.975, 1.128] | 0.199 |
| log-volume of LNCCIs | | | 1.066 [1.035, 1.099] | < 0.001 | 1.055 [1.025, 1.087] | < 0.001 |
| presence of SNCIs | | | 1.055 [0.980, 1.136] | 0.156 | 1.036 [0.965, 1.113] | 0.330 |
| log-volume of SNCIs | | | 1.030 [0.978, 1.085] | 0.262 | 1.020 [0.970, 1.072] | 0.442 |
| presence of MBs | | | 1.104 [1.011, 1.207] | 0.028 | 1.079 [0.991, 1.176] | 0.079 |
| count of MBs | | | 1.017 [0.987, 1.047] | 0.266 | 1.013 [0.985, 1.042] | 0.372 |
| log-volume of WMLs | | | 1.045 [1.019, 1.071] | < 0.001 | 1.043 [1.018, 1.068] | < 0.001 |
| nBV (per 100cm ³) | | | 0.945 [0.914, 0.978] | 0.001 | 0.951 [0.919, 0.983] | 0.003 |

* Sex, atrial fibrillation type, history of coronary heart disease and obstructive sleep apnea were eliminated from the final, reduced clinical model.

† The back-transformed model-based estimates β_{mult} represent multiplicative effects on sNfL (e.g., $\beta_{\text{mult}} = 1.325$ for age denotes an average 1.325-fold increase in sNfL concentration, that is an average 32.5% sNfL increase, per 10 years older age.)

AIC, Akaike's information criterion; BMI, body mass index; MAP, mean arterial pressure; TIA, transient ischemic attack; LNCCIs, large non-cortical or cortical infarcts; SNCIs, small non-cortical infarcts; MBs, microbleeds; WMLs, white matter lesions; nBV, normalized brain volume

Table 3: Association of log-sNfL with measures of cognitive function

| Cognitive measures (N = 1,363) | univariable | | age-adjusted | | multivariable clinical model* | | multivariable MRI model† | | multivariable combined model‡ | |
|-----------------------------------|-------------------------|---------|-------------------------|---------|-------------------------------|---------|--------------------------|---------|-------------------------------|---------|
| | $\beta^§$ [95% CI] | p-value | $\beta^§$ [95% CI] | p-value | $\beta^§$ [95% CI] | p-value | $\beta^§$ [95% CI] | p-value | $\beta^§$ [95% CI] | p-value |
| MoCA | -0.93 [-1.17, -0.69] | < 0.001 | -0.37 [-0.65, -0.10] | 0.008 | -0.23 [-0.51, 0.05] | 0.114 | -0.22 [-0.51, 0.06] | 0.123 | -0.15 [-0.44, 0.14] | 0.307 |
| TMT-A | -0.11 [-0.13, -0.10] | < 0.001 | -0.04 [-0.06, -0.02] | < 0.001 | -0.04 [-0.06, -0.02] | < 0.001 | -0.03 [-0.04, -0.01] | 0.009 | -0.03 [-0.04, -0.01] | 0.012 |
| TMT-B | -0.06 [-0.07, -0.05] | < 0.001 | -0.02 [-0.03, -0.01] | < 0.001 | -0.02 [-0.03, -0.01] | < 0.001 | -0.01 [-0.02, -0.00] | 0.015 | -0.01 [-0.02, -0.00] | 0.023 |
| SVF | -1.56 [-2.00, -1.12] | < 0.001 | -0.46 [-0.97, 0.05] | 0.076 | -0.29 [-0.81, 0.24] | 0.283 | -0.14 [-0.67, 0.38] | 0.587 | -0.09 [-0.62, 0.45] | 0.752 |
| DSST | -6.95 [-8.07, -5.83] | < 0.001 | -2.40 [-3.64, -1.16] | < 0.001 | -1.75 [-2.96, -0.54] | 0.005 | -0.98 [-2.23, 0.27] | 0.124 | -0.84 [-2.05, 0.37] | 0.175 |
| PC1 | -0.98 [-1.11, -0.84] | < 0.001 | -0.34 [-0.49, -0.20] | < 0.001 | -0.27 [-0.41, -0.12] | < 0.001 | -0.18 [-0.33, -0.03] | 0.016 | -0.16 [-0.31, -0.01] | 0.032 |

* adjusted for age, sex, education level, history of hypertension, diabetes mellitus, stroke or TIA, coronary heart disease, peripheral artery disease, heart failure, obstructive sleep apnea, BMI, smoking status, alcohol consumption

† adjusted for age, normalized brain volume, presence and volume of small non-cortical infarcts, presence and volume of large non-cortical or cortical infarcts, burden of MBs, volume of white matter lesions

‡ adjusted for age, sex, education level, history of hypertension, diabetes mellitus, stroke or TIA, coronary heart disease, peripheral artery disease, heart failure, obstructive sleep apnea, BMI, smoking status, alcohol consumption, normalized brain volume, presence and volume of small non-cortical infarcts, presence and volume of large non-cortical or cortical infarcts, burden of MBs, volume of white matter lesions

§ The model-based estimates β represent additive effects on test score (e.g., $\beta = -0.93$ for the association of log-sNfL with MoCA denotes an average decrease of 0.93 points in the MoCA score per unit higher log-sNfL, or an average decrease of approx. 0.09 points in the MoCA score per 10% higher sNfL concentration)

MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; SVF, Semantic Verbal Fluency; DSST, Digit Symbol Substitution Test; PC1, first principal component

Figure legends

Figure 1: Boxplots of sNfL distribution stratified to CHA₂DS₂-VASc score

Figure 2: Multiplicative effect sizes of the association of clinical and MRI variables with sNfL from the combined model

Figure 3: Scatter plot of the association of (A) mean arterial pressure and (B) normalized brain volume with sNfL. The solid line represents the predicted values from the combined clinical and MRI model and the dashed lines represent the 95% pointwise confidence intervals.

Figure 4: Model-based estimates for the association of log-sNfL with PC1

Figure 5: Scatter plot of the age-adjusted association of sNfL with PC1. The solid line represents the model-based predicted values and the dashed lines represent the pointwise 95% confidence intervals.

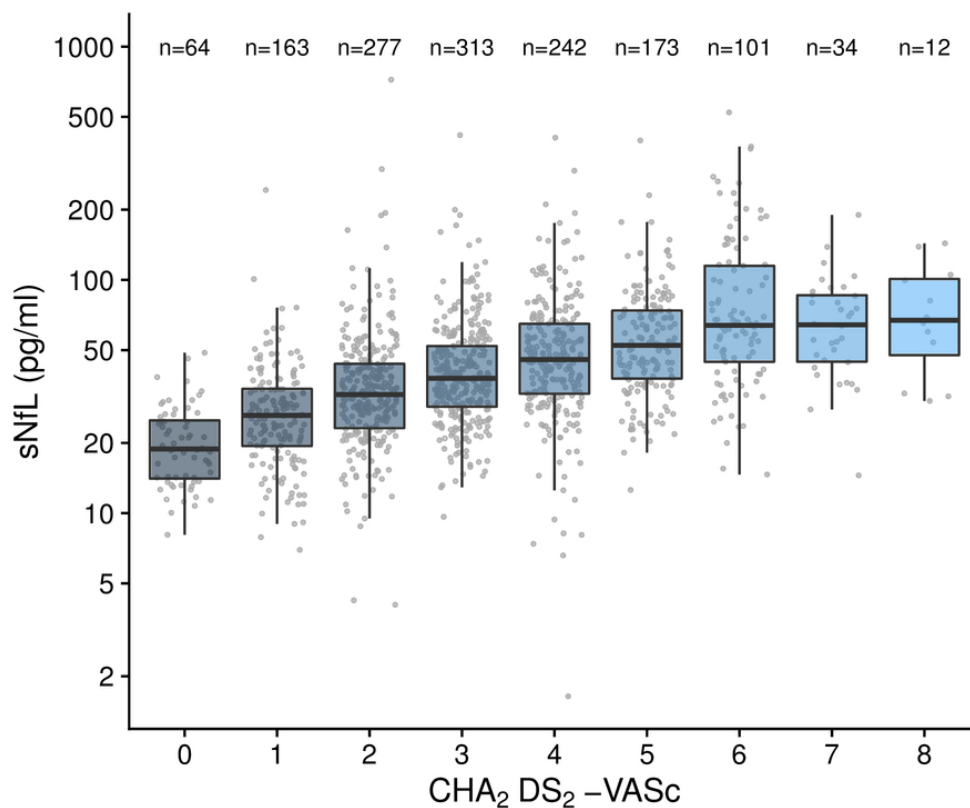


Figure 1: Boxplots of sNfL distribution stratified to CHA₂DS₂-VASc score

76x63mm (300 x 300 DPI)

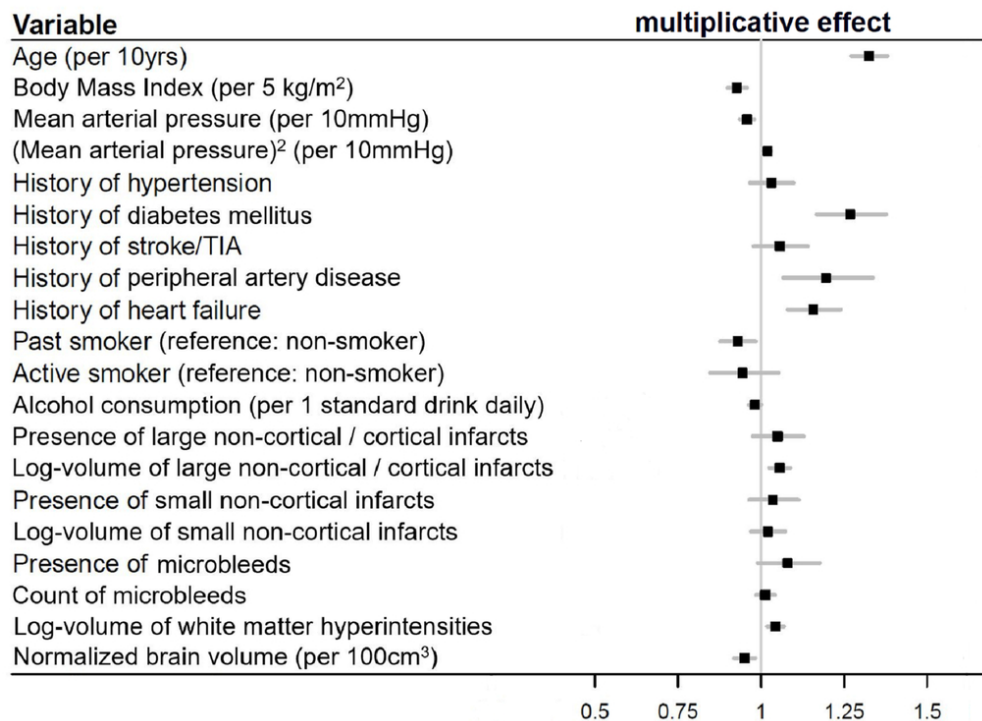


Figure 2: Multiplicative effect sizes of the association of clinical and MRI variables with sNfL from the combined model

86x63mm (300 x 300 DPI)

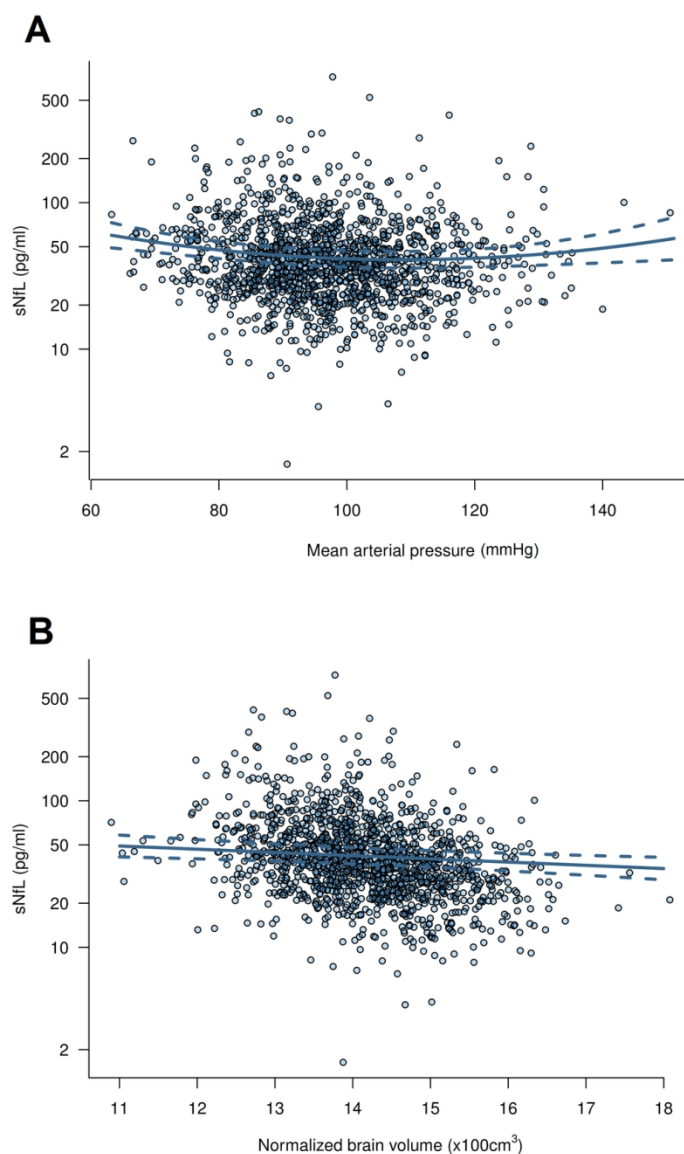


Figure 3: Scatter plot of the association of (A) mean arterial pressure and (B) normalized brain volume with sNfL. The solid line represents the predicted values from the combined clinical and MRI model and the dashed lines represent the 95% pointwise confidence intervals.

92x151mm (300 x 300 DPI)

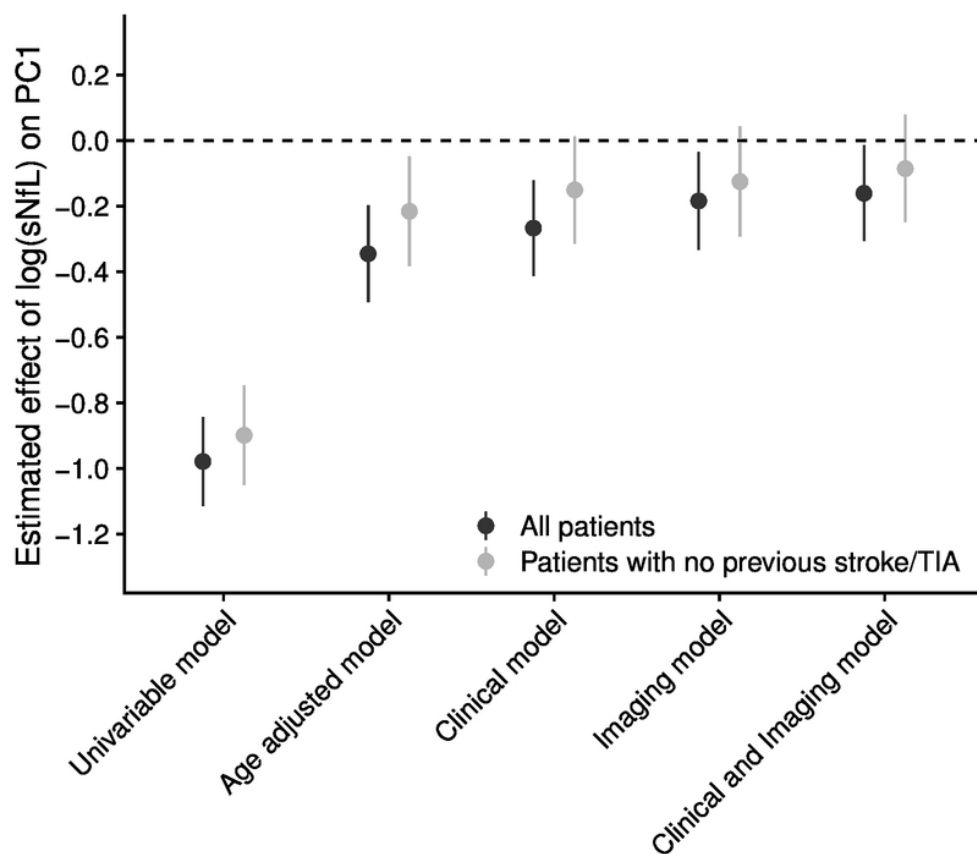


Figure 4: Model-based estimates for the association of log-sNfL with PC1

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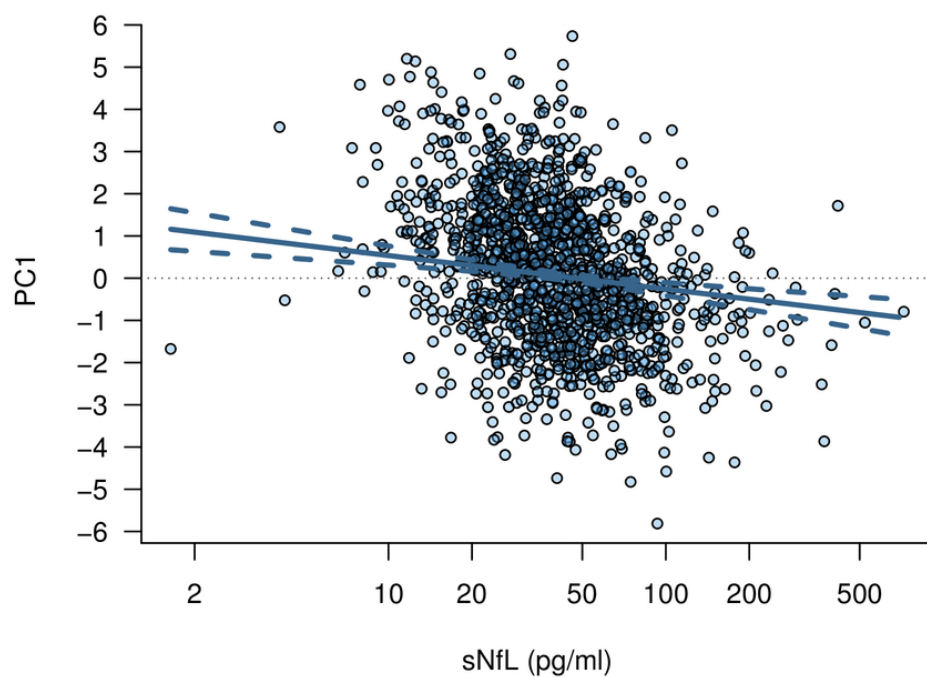


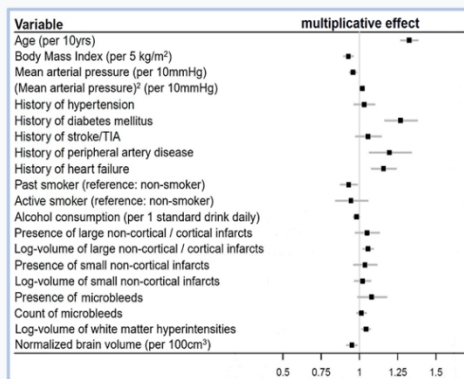
Figure 5: Scatter plot of the age-adjusted association of sNfL with PC1. The solid line represents the model-based predicted values and the dashed lines represent the pointwise 95% confidence intervals.

76x63mm (300 x 300 DPI)

Serum neurofilament light in 1,379 patients with atrial fibrillation a cross-sectional analysis from Swiss-AF

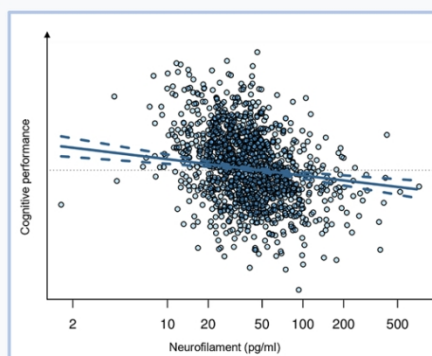
Analysis A

Clinical and MRI correlates of neurofilament



Analysis B

Neurofilament and cognitive performance



Graphical abstract

101x75mm (300 x 300 DPI)

Polymeris et al.

Serum neurofilament light in atrial fibrillation: clinical, neuroimaging and cognitive correlates

Abbreviated Summary

In patients with atrial fibrillation we show that age, diabetes, heart failure, peripheral artery disease and subclinical ischemic brain lesions are associated with serum levels of neurofilament light chain, a biomarker of neuronal loss. Higher neurofilament levels were associated with smaller brain volume and worse cognitive performance.